Indian Academy of Pediatrics (IAP)

nRICH

Newer **R**esearch and recommendations **I**n **C**hild **H**ealth

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UNDER THE AUSPICES OF THE IAP ACTION PLAN 2023

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Dear fellow IAPans,

nRICH

Newer **R**esearch and recommendations **I**n **C**hild **H**ealth-aims to bring you the abstracts of some of the breakthrough developments in pediatrics, carefully selected from reputed journals published worldwide.

Expert commentaries will evaluate the importance and relevance of the article and discuss its application in Indian settings. nRICH will cover all the different subspecialities of pediatrics from neonatology, gastroenterology, hematology, adolescent medicine, allergy and immunology, to urology, neurology,vaccinology etc. Each issue will begin with a concise abstract and will represent the main points and ideas found in the originals. It will then be followed by the thoughtful and erudite commentary of Indian experts from various subspecialties who will give an insight on way to read and analyze these articles.

I'm sure students, practitioners and all those interested in knowing about the latest research and recommendations in child health will be immensely benefitted by this endeavor which will be published online on every Monday.

Happy reading!

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Levetiracetam versus phenytoin for second-line treatment of paediatric convulsive status epilepticus (EcLiPSE): a multicentre, open-label, randomised trial

Arun Bansal, Siva Vyasam

BASED ON ARTICLE

Mark D Lyttle, Naomi E A Rainford, Carrol Gamble, Shrouk Messahel, Amy Humphreys, Helen Hickey, Kerry Woolfall, Louise Roper, Joanne Noblet, Elizabeth D Lee, Sarah Potter, Paul Tate, Anand Iyer, Vicki Evans, Richard E Appleton, with support of Paediatric Emergency Research in the United Kingdom & Ireland (PERUKI) collaborative.* Lancet. 2019. 393(10186):2125-2134. http://dx.doi.org/10.1016/S0140-6736(19)30724-X

ABSTRACT

Background: Phenytoin is the recommended second-line intravenous anticonvulsant for treatment of paediatric convulsive status epilepticus in the UK; however, some evidence suggests that levetiracetam could be an effective and safer alternative. This trial compared the efficacy and safety of phenytoin and levetiracetam for second-line management of paediatric convulsive status epilepticus.

Methods: This open label randomised clinical trial was undertaken at 30 UK emergency departments at secondary and tertiary care centres. Participants aged 6 months to under 18 years, with convulsive status epilepticus requiring second-line treatment, were randomly assigned (1:1) using a computer-generated randomisation schedule to receive levetiracetam (40 mg/kg over 5 min) or phenytoin (20 mg/kg over at least 20 min), stratified by centre. The primary outcome was time from randomisation to cessation of convulsive status epilepticus, analysed in the modified intention-to-treat population (excluding those who did not require second-line treatment after randomisation and those who did not provide consent). This trial is registered with ISRCTN, number ISRCTN22567894.

Findings: Between July 17, 2015, and April 7, 2018, 1432 patients were assessed for eligibility. After exclusion of ineligible patients, 404 patients were randomly assigned. After exclusion of those who did not require second-line treatment and those who did not consent, 286 randomised participants were treated and had available data: 152 allocated to levetiracetam, and 134 to phenytoin. Convulsive status epilepticus was terminated in 106 (70%) children in the levetiracetam group and in 86 (64%) in the phenytoin group. Median time from randomisation to cessation of convulsive status epilepticus was 35 min (IQR 20 to not assessable) in the levetiracetam group and 45 min (24 to not assessable) in the phenytoin group (hazard ratio 1·20, 95% CI 0·91–1·60; p=0·20). One participant who received levetiracetam followed by phenytoin died because of catastrophic cerebral oedema unrelated to either treatment. One participant who received phenytoin had serious adverse reactions related to study treatment (hypotension considered to be immediately life-threatening [a serious adverse reaction] and increased focal seizures and decreased consciousness considered to be medically significant [a suspected unexpected serious adverse reaction]).

Interpretation: Although levetiracetam was not significantly superior to phenytoin, the results, together with previously reported safety profiles and comparative ease of administration of levetiracetam, suggest it could be an appropriate alternative to phenytoin as the first-choice, second-line anticonvulsant in the treatment of paediatric convulsive status epilepticus

SUMMARY

Background: In the United Kingdom, phenytoin is recommended as a second-line intravenous anticonvulsant for the treatment of paediatric convulsive status epilepticus; however, some research suggests that levetiracetam may be a more effective and secure alternative. This trial compared the efficacy and safety of phenytoin and levetiracetam for the second-line treatment of paediatric convulsive status epilepticus.

About the Study: Emergency treatment with Levetiracetam or Phenytoin in convulsive Status Epilepticus in children (EcLiPSE). A multicenter, open label randomised clinical trial was carried out in the United Kingdom. From 17 July 2015 to 7 April 2018, children enrolled in 30 Emergency Departments in the United Kingdom were randomly assigned to either Levetiracetam (40mg/kg over 5 minutes - MAX Dose 2.5g) or Phenytoin (20mg/kg over 20 minutes - MAX Dose 2g). They included children ranging in age from 6 months to 18 years who had convulsive status epilepticus and required second-line treatment. Exclusion criteria included having myoclonic or non-convulsive status epilepticus, being pregnant, having a contraindication or allergy to levetiracetam or phenytoin, having established renal failure, having received a second line anticonvulsant during the presenting episode of convulsive status epilepticus before screening, being enrolled in the EcLiPSE trial, and not requiring second-line treatment. The primary outcome was the time from randomization to the cessation of all visible signs of convulsive activity, defined as the cessation of all continuous rhythmic clonic activity by the treating clinician. Secondary outcomes included the need for additional anticonvulsants to manage convulsive status epilepticus following trial treatment administration, the need for RSI due to ongoing convulsive status epilepticus, the need for critical care admission, and serious adverse reactions (including death, Stevens-Johnson syndrome, rash, airway complications, cardiovascular instability, extravasation injury, and extreme agitation). A total of 404 patients were assigned at random. For 93 patients, second-line treatment was not required. 286 patients were assigned and treated at random. The Levetiracetam group had 152 children and the Phenytoin group had 134 children. In the levetiracetam group, 106 children (70%) and in the phenytoin group, 86 children (64%) had their convulsive status epilepticus terminated, respectively. The median time from randomization to the start of the infusion in the levetiracetam group was 11 minutes (range: 8 to 15 minutes), compared to 12 minutes in the phenytoin group (Range 8 – 17min). The median time from randomization to the termination of convulsive status epilepticus in the levetiracetam group was 35 minutes, whereas the phenytoin group took 45 minutes, with HR 1.20; 95% CI 0.91 - 1.60; p = 0.20. The levetiracetam group experienced 20 adverse events in 16 patients (12%), whereas the phenytoin group experienced 23 events in 18 patients (14%). Agitation was the most common adverse event. This occurred with 11 patients (8%) in the levetiracetam group and 4 patients (3%) in the phenytoin group.

Strengths: The largest multicenter randomised controlled trial comparing levetiracetam to phenytoin for the treatment of paediatric convulsive status epilepticus that had not responded to first-line treatment was conducted. A computer-generated randomization sequence was created by an independent statistician who had no connection to the study. Performed site checks on a regular basis to ensure that the proper number of envelopes were used, that the envelopes were in good condition, and that the sequential numbering system was followed. All adverse events were evaluated by the principal investigator at each participating site. The baseline characteristics of participants were well balanced across groups.

Limitation: An open-label trial as a double-blind design was too complicated due to the significantly different infusion rates of the two drugs and the potentially fatal nature of convulsive status epilepticus. Instead of using fixed timepoints to assess cessation of convulsive status epilepticus, researchers used cessation of all signs of continuous, rhythmic clonic activity. Using an electroencephalogram (EEG) to determine the time of cessation of convulsive status epilepticus would have been more precise, despite the fact that it was not possible. It is unclear whether any patients experienced non-convulsive status epilepticus in the absence of EEGs. Due to the timing of randomization, many patients developed convulsive status epilepticus prior to receiving trial treatment. This study was not powered to detect a difference in the frequency of major adverse events between groups.

What is the way forward? It is well understood that the longer a seizure lasts in a convulsive status epilepticus, the more difficult it is to stop it and the greater the likelihood of developing a neurodisability. Levetiracetam can be administered faster (5-10 minutes) than phenytoin (at least 20 minutes), which may allow it to end convulsive status epilepticus sooner than phenytoin. While clinicians may be hesitant to administer a loading dose of phenytoin to children in convulsive status epilepticus who are receiving oral maintenance phenytoin due to the possibility of cardiovascular toxicity, there do not appear to be any similar concerns for levetiracetam. In the treatment of convulsive status epilepticus, the ease with which drugs can be prepared and administered is also important. Due to the calculations required in reconstituting phenytoin, the number of vials required with phenytoin, and the procedures required for its administration, clinical teams in the EcLiPSE trial reported that levetiracetam was easier to prepare and administer than phenytoin. Levetiracetam is also less dangerous than phenytoin, with a lower incidence of hypotension and respiratory depression.